

US application Serial No. 09/891/750
Attorney Docket No. QA0239A-CIP

REMARKS

Status of the Claims

Claims 52-95 are pending.

In the present Amendment, Claims 52-65, 67-69, 83, 84, 86, 87, 89 – 95 have been cancelled. Claims 66 and 70 have been written in independent form and Claims 66, 70-78, and 82 have been amended in response to rejections under 35 U.S.C. 112. The amendments have not added new matter, nor have they broadened the scope of the claims.

Claim Objections

New Matter

The Examiner requires cancellation of the replaced chemical structures on pages 104 and 105 of the Specification contending that the structures constitute new matter since there was no explanation for the changes.

The chemical structure was replaced on page 104 because the original structure was incorrectly copied into the table, thereby leaving the amide of the benzamide group outside the table display. With regard to the replaced chemical structure on page 105, the structure was incompletely drawn so as to omit the aromaticity of both the pyridine and phenyl rings. Accordingly, both structures were replaced in the previous amendment in order to correct typographical errors in the original specification.

In view of the above, Applicants assert that the corrected chemical structures do not constitute new matter and request withdrawal of this rejection.

Section 112 Rejections

Definiteness Rejections

Claims 52-95 are rejected under 35 U.S.C. 112, second paragraph, as the Examiner contends that there is ambiguity between the definition of "prodrug" and the definition of various R groups including esters, alkoxycarbonyl, etc. and "therefore it is not clear what is the difference between these variable groups and the prodrug groups." Applicants do not agree as it is believed that one of skill in the art would readily be able to differentiate the various R groups from prodrugs of the compositions of the instant invention. However, in order to expedite the prosecution of this

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application, the claims 66 and 70-77 have been amended to delete the term "prodrug". It is believed this amendment fully addresses the Examiner's rejection.

Claim 53 has been rejected for indefiniteness, as the Examiner contends it is uncertain whether the proviso of Claim 53 corresponds to the proviso applied to Claim 52, or is applied to claim 53. Applicants have cancelled these claims and believe the rejection is moot.

The Examiner contends that claims 54-56 are indefinite "as they recite R² choice without reciting Z as NR¹R²." Applicants do not understand this rejection. Claims 54-56 ultimately depend from Claim 52 (not 53). However, since Applicants have cancelled these claims, the rejection is moot.

Description and Enablement Rejections

The Examiner has rejected claims 52-95 under 35 U.S.C. 112, first paragraph, contending that there is no support in the specification for the term, stereoisomers. Applicants do not agree, as there is ample basis in the terms "enantiomers" and "diastereomers". However, in order to expedite the prosecution of this application, the claims have been amended to delete the word "stereoisomers". Accordingly, Applicants believe the rejection is now moot.

Claims 82-85 and 87-96 have also been rejected under 35 U.S.C. 112, first paragraph as the Examiner contends that the specification does not "reasonably provide enablement for treating any or all p38 mediated diseases/disorder and/or TNF- α mediated disorders." Applicants amend the claims and traverse in part.

Claim 88 is directed to a method of inhibiting TNF- α expression in mammals. Support for this is provided by the assays described on pages 38-40 of the specification. It is well accepted in the art that activity in these assays is predictive of in vivo activity. Accordingly, it is requested that the enablement rejection of Claim 88 be withdrawn.

While Applicants do not agree that there is not adequate support for in order to enable the treatment of p38-mediated disease and/or TNF- α related disorders, in order to facilitate the prosecution of this application, Applicants have amended claim 82 to specify a method of treating rheumatoid arthritis, and canceled dependent claims 83, 84, 90, 91, 94 and 95. Accordingly, it is believed that the Examiner's rejection for lack of enablement based on these claim is now moot

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Section 102 and 103 Rejections

The Examiner has rejected Claims 52-53, 61, 69-70 and 78 under 35 U.S.C. 102(b) or alternatively under 35 U.S.C. 103(a) as being anticipated by US 3,625,979 ("Heimberger"). The Examiner contends that Heimberger teaches several trisubstituted trazines, for use as anti-inflammatory agents and directs attention to Applicants to Formula I in column I as well as examples 1-13, particularly examples 6, 10 12(?), and 12. Applicants amend the present claims and traverse the rejection.

Claims 51-69 have been cancelled, claim 70 has been re-written in independent form, and claims 72-76 and 78 have been amended to depend from claim 70. As amended the claims require that the Z substituent of Applicants broadest generic is not a heterocyclic ring (see the definition of $N(R_1)(R_2)$ in amended claim 70).

According to the MPEP 2131.02, "in a genus-species situation when the compound is not specifically named, but instead it is necessary to select portions of teaching with a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a general chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated." Ex part A, 17 USPQ2d 1716 (Bd. Pat App. & Inter. 1990). Further, one of ordinary skill must "at once envisage" the specific compounds within the generic chemical formula to anticipate the compounds. It is suggested that looking to the preferred embodiments is an indication of anticipation. In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962). One of ordinary skill cannot envisage Applicants' specific compounds from the broad generic disclosed in Heimberger.

Accordingly, in the present case there are a large number of possible species disclosed within Heimberger broad generic described by Formula I (See Heimberger, abstract). It would be impossible to select the various substituents from the alternatives suggested in the Heimberger Markush groups to arrive at Applicants' claimed compositions without the aid of hindsight. Additionally, there are no preferred groups or examples throughout Heimberger that would lead one of skill in the art to envisage Applicants' claimed compounds. Indeed, the closest Heimberger examples (See Heimberger, Examples 6, 10, 11 and 12) disclose only heterocyclic rings in the Z position, directing the attention of one of skill in the art away from Applicants' compounds.

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Accordingly, Applicants' amended claims are not anticipated by Heimberger, nor are they obvious over Heimberger.

The Examiner contends that claims 52-53, 61, 69-70 and 78 obvious over Heimberger for the reasons already cited in the 102 rejection above, and additionally, because the claims (including claims 70 and 78) allegedly require Z and or R¹¹ to be a heterocyclic ring, especially homopiperazine. Applicants respectfully traverse.

As discussed above, unlike the exemplified Heimberger compositions, the Z group described in Applicants' claimed compositions (i.e. claims 70-76 and 78) exclude the possibility that Z is a heterocyclic ring. Moreover, there is no suggestion or motivation in Heimberger to provide Applicants monoarylamino triazines. Accordingly, Heimberger's examples which contain a ring in the corresponding Z position do not render Applicants' compositions obvious.

Applicants respectfully request that the Examiner withdraw the novelty and obviousness rejections of claims 70-76 and 78 over Heimberger.

Section 103 Rejection

Claims 51-65, 67-75, 79-80 and 86 were rejected under Section 103(a) in view of Daeyaert *et al.*, US Pat. No. 6,150,360. The Examiner renews his rejection of the claims and does not accept Applicants assertion that the biarylamino compounds of Daeyaert do not provide motivation to one of skill in the art to obtain Applicants' claimed compositions. The Examiner replies that Daeyaert teaches equivalency of biarylamino triazines to monoarylamino triazines because generically claimed compounds are considered to be equivalent to the exemplified compounds. Applicants respectfully traverse.

As discussed previously, the selections for R², R³ and R¹⁴ in the present claims 70 describe monoarylamino triazine structures, not biarylamino triazines. Daeyaert *neither exemplifies nor includes monoarylamino triazines in their broadest generic structure*. Accordingly, contrary to the Examiner's argument, Daeyert has provided no teaching or suggestion that it would be desirable to replace one of the aryl/heteroaryl groups with a non-aromatic ring or non-ring group.

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Therefore, it is submitted that Section 103 may not be applied to new claims 70 -75, 79-80 and 86 based on Daeyert. Compare, *e.g.*, *Ex parte Ligett*, 121 USPQ 324, 326 (Bd. Pat. App. 1958) (holding an alkyl ester of N-phenyl maleamic acid unobvious over an alkyl ester of N-naphthyl maleamic acid because nothing in the art suggested the phenyl derivative would be expected to be as effective as the naphthyl derivative – both compounds used for fungicides).

Accordingly, Applicant request that the obviousness rejection of claims 70-75, 79-80 and 86 over Daeyert be withdrawn.

Applicants believe the claims are in condition for allowance.

FEES

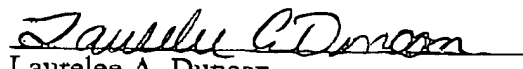
No fees should be due.

SUMMARY

In view of the foregoing, it is requested that this case proceed to issuance. The Examiner is invited to contact the undersigned if it is believed prosecution could be expedited. Attached hereto is a "Version with Markings to Show Changes Made" (i.e., showing the corrections to the specification).

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
609-252-5323

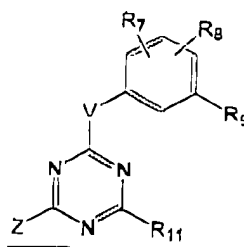

Laurelee A. Duncan
Attorney for Applicants
Reg. No. 44,096

Date: May 3, 2003

Signed July 30, 2003

Marked-Up Version to Show Changes to the Claims

66 (Amended). A compound of Formula (I).



I

66. ~~A compound of Claim 52 or a stereoisomer, or an enantiomer,~~
~~diastereomer, tautomer, or pharmaceutically-acceptable salt, prodrug, or solvate thereof~~
solvate thereof, wherein:

wherein V is chosen from $-\text{CHR}^5$ -, $-\text{NR}^5$ -, $-\text{O}$ -, and $-\text{S}$ -;

Z is chosen from halogen, alkyl, substituted alkyl, aryl, substituted aryl,
cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, $-\text{SR}^3$, $-\text{OR}^3$, and
 $-\text{N}(\text{R}^1)(\text{R}^2)$;

$-\text{N}(\text{R}^1)(\text{R}^2)$ taken together may form a heterocyclyl or substituted heterocyclyl; or

R^1 is chosen from hydrogen, alkyl and substituted alkyl; and

R^2 is chosen from hydrogen, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl,
cycloalkyl, substituted cycloalkyl, heterocyclyl and substituted heterocyclyl;

R^3 is chosen from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl,
cycloalkyl, substituted cycloalkyl, heterocyclyl and substituted heterocyclyl;

R^5 is chosen from hydrogen and alkyl, or when attached to a nitrogen atom, R^5
taken together with R^7 may form a fused heterocyclyl or substituted heterocyclyl;

R^7 is chosen from hydrogen, $-\text{N}(\text{R}^{31})(\text{R}^{32})$, halogen, cyano, alkyl, substituted
alkyl, alkoxy, and alkylthio, or when V is $-\text{NR}^5$, $-\text{R}^5$ and R^7 taken together may form a
fused heterocyclyl or substituted heterocyclyl;

R^8 is chosen from hydrogen and halogen;

R^9 is chosen from $-\text{CO}_2(\text{alkyl})$, $-\text{C}(\text{O})\text{N}(\text{R}^{31})(\text{R}^{32})$, $-\text{SO}_2\text{N}(\text{R}^{31})(\text{R}^{32})$,
 $-\text{N}(\text{R}^{33})\text{SO}_2\text{R}^{34}$, $-\text{C}(\text{O})\text{N}(\text{R}^{33})\text{N}(\text{R}^{31})(\text{R}^{32})$, $-\text{N}(\text{R}^{33})\text{C}(\text{O})\text{R}^{34}$, $-\text{CH}_2\text{N}(\text{R}^{33})\text{C}(\text{O})\text{R}^{34}$,
 $\text{N}(\text{R}^{31})(\text{R}^{32})$, $-\text{CH}_2\text{OC}(\text{O})\text{R}^{34}$, $\text{C}_{1-6}\text{alkyl}$, substituted alkyl, cycloalkyl, substituted
cycloalkyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, and $-\text{C}(\text{O})\text{R}^{10}$;

provided, however, that when R^9 is CH_3 or NH_2 , then neither R^2 nor R^{14} is *para*-cyano-phenyl;

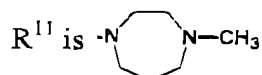
or R^8 and R^9 taken together may form $-C(O)N(R^{33})CH_2-$ or $-C(O)N(R^{33})C(O)-$;

R^{10} is chosen from heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkyl, and substituted alkyl;

R^{31} and R^{33} are independently chosen from hydrogen, alkyl, and substituted alkyl;

R^{32} is chosen from hydrogen, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, aryloxy, heterocyclyl and substituted heterocyclyl;

R^{34} is chosen from alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclyl and substituted heterocyclyl;



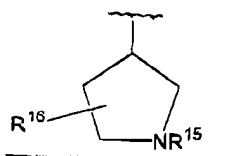
R^{12} is chosen from hydrogen, alkyl, and substituted alkyl;

R^{13} is $-(CH_2)_mR^{14}$;

$-N(R^{12})(R^{13})$ taken together may form a heterocyclyl or substituted heterocyclyl;

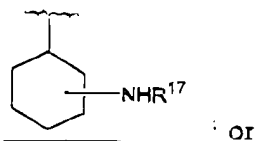
m is 0, 1, 2 or 3;

R^{14} is chosen from hydrogen, alkyl, substituted alkyl, $-C(O)N(R^{31})(R^{32})$, $-N(R^{33})C(O)R^{34}$, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, and



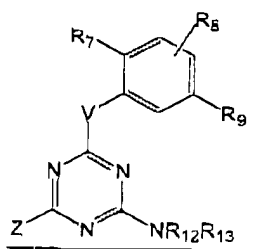
R^{15} is chosen from hydrogen, alkyl, substituted alkyl, alkenyl, $-C(O)$ -alkyl, $-C(O)$ -substituted alkyl, $-C(O)$ -aryl, $-C(O)$ -substituted aryl, $-C(O)$ -alkoxy, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclyl and substituted heterocyclyl;

R^{16} is chosen hydrogen, alkyl, substituted alkyl, and



R^{17} is chosen from hydrogen, alkyl, substituted alkyl, -C(O)-alkyl, -C(O)-substituted alkyl, -C(O)-aryl, and -C(O)-substituted aryl.

70. (Amended). A compound having the formula.



~~70. A compound according to Claim 69 or a stereoisomer, or a enantiomer, diastereomer, tautomer, or pharmaceutically-acceptable salt, prodrug, or solvate thereof, or solvate thereof, wherein:~~

~~wherein:~~

V is chosen from -CHR⁵-, -NR⁵-, -O-, and -S-;

Z is halogen, alkyl, -N(R¹)(R²), or alkyl substituted with one to two of -N(R³¹)(R³²), alkoxy, alkylthio, halogen, cyano, carboxyl, hydroxyl, -SO₂-alkyl, -CO₂-alkyl, -C(O)-alkyl, nitro, cycloalkyl, substituted cycloalkyl, -C(O)-N(R³¹)(R³²), and/or -NH-C(O)-alkyl;

R¹ is hydrogen or methyl;

R² is alkyl of 1 to 8 carbon atoms;

R³ is chosen from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclyl and substituted heterocyclyl;

R⁵ is chosen from hydrogen and alkyl of 1 to 4 carbon atoms;

R⁷ is chosen from hydrogen, amino, aminoC₁₋₄alkyl, halogen, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, and alkylthio;

R^8 is attached to any available carbon atom of the phenyl ring and is chosen from hydrogen and halogen;

R^9 is chosen from $-C(O)N(R^{31})(R^{32})$, $-SO_2N(R^{31})(R^{32})$, $-N(R^{33})SO_2R^{34}$, $-C(O)N(R^{33})N(R^{31})(R^{32})$, $-N(R^{33})C(O)R^{34}$, $-CH_2N(R^{33})C(O)R^{34}$, $-N(R^{31})(R^{32})$, $-CH_2OC(O)R^{34}$, heterocyclyl, and substituted heterocyclyl; or

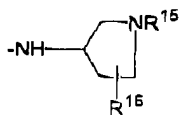
R^8 and R^9 taken together may form $-C(O)N(R^{33})CH_2-$ or $-C(O)N(R^{33})C(O)-$;

R^{31} and R^{33} are independently chosen from hydrogen, alkyl, and substituted alkyl;

R^{32} is chosen from hydrogen, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, aryloxy, heterocyclyl and substituted heterocyclyl;

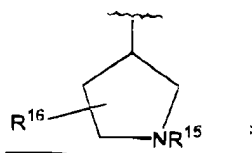
R^{34} is chosen from alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclyl and substituted heterocyclyl;

$N(R^{12})(R^{13})$ taken together form a monocyclic heterocyclyl or substituted heterocyclyl of 5 to 7 atoms having 1, 2 or 3 additional nitrogen atoms, $-NH$ -alkyl wherein alkyl is of 1 to 4 carbon atoms, or



m is 0, 1, 2 or 3;

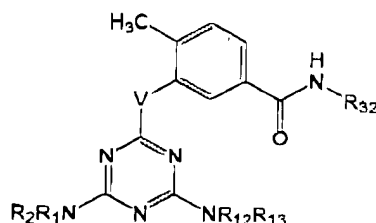
R^{14} is chosen from hydrogen, alkyl, substituted alkyl, $-C(O)N(R^{31})(R^{32})$, $-N(R^{33})C(O)R^{34}$, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl and



R^{15} and R^{16} are independently hydrogen or methyl; and

R^{17} is chosen from hydrogen, alkyl, substituted alkyl, $-C(O)$ -alkyl, $-C(O)$ -substituted alkyl, $-C(O)$ -aryl, and $-C(O)$ -substituted aryl.

71 (Amended). A compound of Claim 70 or ~~astereoisomer~~, enantiomer, diastereomer, tautomer, or pharmaceutically-acceptable salt, ~~prodrug~~, or solvate thereof, having the formula:



72 (Amended). The compound of claim ~~6970~~ or ~~astereoisomer~~, enantiomer, diastereomer, tautomer, or pharmaceutically-acceptable salt, ~~prodrug~~, or solvate thereof, wherein:

R^7 is halogen, methyl, methoxy, halogen, or cyano.

73 (Amended). The compound of claim ~~6970~~ or a stereoisomer, enantiomer, diastereomer, tautomer, or pharmaceutically-acceptable salt, ~~prodrug~~, or solvate thereof, wherein:

R^9 is $C(=O)NH_2$, $C(=O)NH(CH_3)$, or $C(=O)NHO(CH_3)$.

74 (Amended). The compound of claim ~~6970~~ or ~~astereoisomer~~, enantiomer, diastereomer, tautomer, or pharmaceutically-acceptable salt, ~~prodrug~~, or solvate thereof, wherein R^7 is methyl and R^9 is $C(=O)NH(CH_3)$ or $C(=O)NHO(CH_3)$.

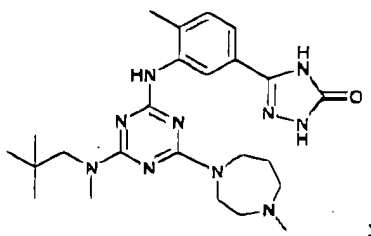
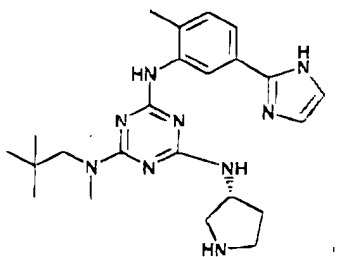
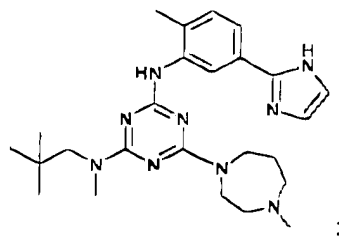
75 (Amended). A compound of Claim ~~6970~~ or ~~astereoisomer~~, enantiomer, diastereomer, tautomer, or pharmaceutically-acceptable salt, ~~prodrug~~, or solvate thereof wherein:

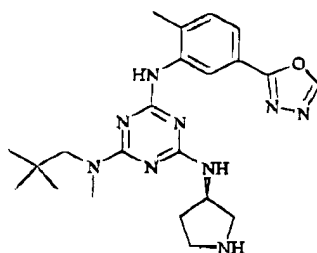
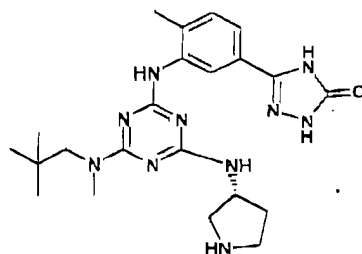
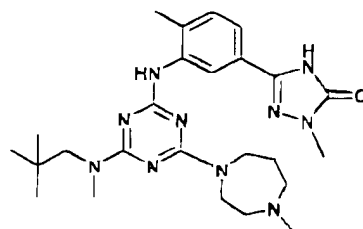
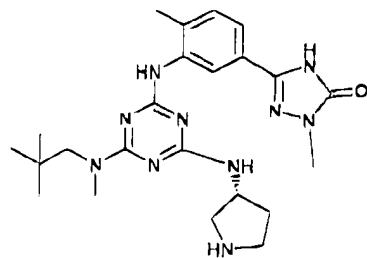
R^9 is chosen from unsubstituted or substituted triazolyl, oxadiazolyl, imidazolyl, thiazolyl and benzimidazolyl.

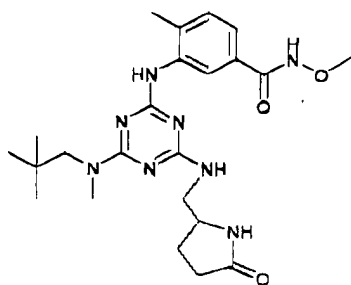
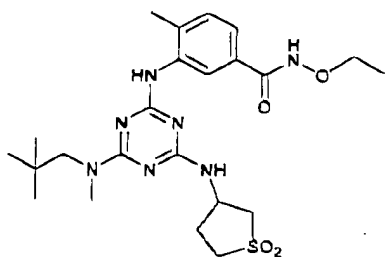
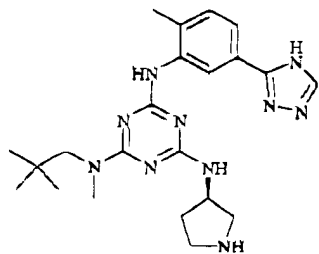
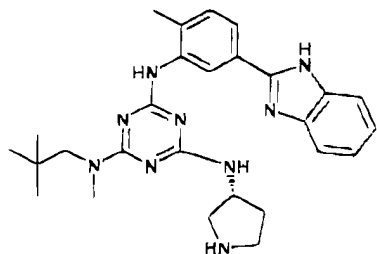
76 (Amended). A compound of Claim 6970 or stereoisomer, enantiomer, diastereomer, tautomer, or pharmaceutically-acceptable salt, prodrug, or solvate thereof wherein:

R⁹ is chosen from substituted or unsubstituted 1,2,4-triazole; substituted or unsubstituted thiazole connected via a C2, C4, or C5 position; substituted or unsubstituted 1,3,4-oxdiazole connected via a 2 or 5 position; and substituted or unsubstituted imidazole connected via a C2, C4, C5, N1 or N3 position.

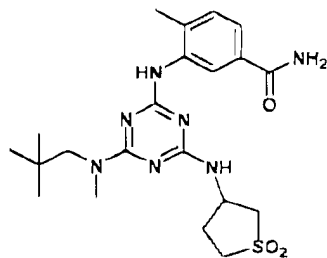
77 (Amended). A compound which is selected from (i):







; and



; or (ii) stereoisomer, enantiomer, diastereomer, tautomer, or pharmaceutically-acceptable salt, prodrug, or solvate of the compound selected from paragraph (i).

78 (Amended). A pharmaceutical composition comprising as an active ingredient, a compound, or a prodrug or salt thereof, according to claim 52, 70, and a pharmaceutically acceptable carrier.

82 (New). A method of treating a condition associated with p38 kinase activity in a mammal, rheumatoid arthritis, the method comprising administering to a mammal in need of such treatment, an effective amount of a composition according to claim 78.